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Applicants : Stedman, *et al.*
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Title : METHODS, COMPOSITIONS AND APPARATUS
FOR DELIVERING HETEROGENIOUS
MOLECULES TO CELLS

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Commissioner for Patents
P.O. Box 1450
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SUGGESTED REQUIREMENT FOR RESTRICTION

Sir:

This paper is in being filed pursuant to 37 CFR 1.142 prior to the earlier of the first Office action on the merits or a requirement for restriction under 35 USC 121.

The **SRR and Election** is on page 2.

A **Courtesy Copy of the Claims** begins on page 3.

Remarks are on page 9.

SUGGESTED RESTRICTION REQUIREMENT

Applicants elect the subject matter of Group I, without traverse.

I. Claims 1 – 18, method for transferring/administering a macromolecular complex to a subject; and

II. Claims 21 – 24, a balloon catheter.

COURTESY COPY OF THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

Claim 1 (original): A method for transferring a macromolecular complex to muscle cells in a subject, said method comprising the steps of
exsanguinating a region of the subject's microvasculature;
delivering a macromolecular complex to the exsanguinated region of the subject's microvasculature under high hydrostatic pressure that transfers the complex to the muscle cells.

Claim 2 (original): The method according to claim 1, further comprising the step of isolating the subject's microvasculature in a limb prior to exsanguination of the limb.

Claim 3 (original): The method according to claim 1, wherein the macromolecular complex is delivered systemically to the venous side of the subject's microvasculature.

Claim 4 (original): The method according to claim 1, wherein the macromolecular complex is a viral vector carrying a target molecule.

Claim 5 (original): The method according to claim 1, wherein the target molecule is selected from the group consisting of an RNA molecule, a transgene, and a chemical moiety.

Claim 6 (original): The method according to claim 1, wherein the transgene is selected from the group consisting of Factor VIII, Factor IX, erythropoietin, a Muscular Dystrophy protein, and a cardiomyopathy protein.

Claim 7 (original): The method according to claim 6, wherein the Muscular Dystrophy protein is selected from the group consisting of dystrophin, utrophin, a sarcoglycan protein, calpain, Fukutin, Fukutin-related protein, telethonin, and laminin.

Claim 8 (original): The method according to claim 1, wherein the hydrostatic high pressure is in the range of about 100 to 500 mm Hg.

Claim 9 (original): The method according to claim 1, wherein the hydrostatic high pressure is rapidly applied by way of at least one low resistance catheter or cannula in either a vein or an artery.

Claim 10 (original): A method of administering a macromolecular complex to a subject having circulating antibodies to said macromolecular complex, said method comprising the steps of:

isolating a region of the subject's microvasculature and exsanguinating the region;

contacting, under high hydrostatic pressure, a subject's microvasculature with a solution comprising a macromolecular complex for delivery to the subject and saline.

Claim 11 (original): The method according to claim 10, further comprising the steps of flushing out residual macromolecular complex and resanguinating the patient.

Claim 12 (original): A method of administering a macromolecular complex to the interstitial space of a subject without activating destructive clotting factors or inflammatory response, said method comprising the steps of :

isolating a region of the subject's microvasculature exsanguinating the region;

contacting, under high hydrostatic pressure, a subject's microvasculature with a solution comprising a macromolecular complex for delivery to the subject and saline.

Claim 13 (original): A method of transferring a macromolecular complex to a limb of a subject, said method comprising the step of:

(a) placing a proximal inflatable tourniquet or balloon catheter for isolating the vasculature of a limb of a subject;

(b) exsanguinating the limb;

(c) applying pressure sufficient to isolate the limb at a girdle between the limb and the trunk of the subject's body; and

(d) infusing the macromolecular complex into the limb at a high hydrostatic pressure.

Claim 14 (original): The method according to claim 13, wherein the macromolecular complex is infused in oxygenated, physiologic saline for a total volume in the range of 20 to 100% of the estimated volume of the extremity.

Claim 15 (original): A method of systemically transferring a macromolecular complex to muscle cells of a subject, said method comprising the step of:

placing a patient under total circulatory arrest using a first heart-lung cannulae and a second heart-lung cannula, each said cannula being placed in a suitable vessel through a cannulation site in each vessel;

lowering the patient's temperature to 15 to 18 °C;

partially exsanguinating and decannulating the patient from the first and second heart-lung cannulae;

introducing a first balloon catheter and a second balloon catheter in the cannulation sites, wherein upon inflation the first balloon catheters occludes the aorta and the second balloon catheter occludes the venae cavae to preclude backflow;

inflating the balloon catheters to a pressure exceeding that applied from cannulae in extremities of the patient; and

simultaneously applying the macromolecular complex in solution to all four of the patient's extremities via the cannulae located therein.

Claim 16 (original): The method according to claim 15, wherein the solution is allowed to dwell for a period of about 5 to 30 minutes.

Claim 17 (original): The method according to claim 15, further comprising the steps of:

flushing out residual macromolecular complex;

withdrawing the balloon catheters;

reinserting the heart-lung cannulae, resanguinating and rewarming the patient.

Claim 18 (original): The method according to claim 15, wherein the balloon catheters comprise an inflatable balloon which extends the length of the cannulae such that upon inflation it expands radially to abut the walls of the vessel, the aortic space and the venae cavae.

Claims 19-20 (canceled).

Claim 21 (original): A balloon catheter for use in infusion of macromolecular complexes into the venous microvasculature of a hypothermic patient, said balloon catheter comprising:

an inflatable balloon (111) having an interior, said balloon being expandable radially without significant distal expansion;

a flexible cannula (125) having a distal end and a proximal end and extending along an axis having a internal channel for the controlled application of fluid under pressure;

wherein said balloon (111) is attached to the cannula at least two points, one point of attachment being adjacent to the distal end of the cannula and a second point of attachment being adjacent to the proximal end of the cannula, such that when inflated, said balloon expands radially to abut the walls of a vessel in which it has been inserted and occludes the aortic space or the venae cavae.

Claim 22 (original): The balloon catheter according to claim 21, wherein the balloon (111) is attached at three or more locations along the cannula.

Claim 23 (original): The balloon catheter according to claim 21, wherein the balloon comprises at least two compartments (142, 144, 146) formed by multiple points of attachment.

Claim 24 (original): The balloon catheter according to claim 23 in which the balloon comprises at least three compartments (142, 144, 146) formed by multiple points of attachment, in which one of said compartments (144) is an intermediate compartment situated along the length of the cannula between two other balloon compartments (142, 146), and in which the distensibility of the intermediate compartment (144) is substantially lower than the distensibility of each of said two other balloon compartments, whereby, when the balloon catheter is disposed in the vena cavae of a patient, with said intermediate compartment (144) situated in the right

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atrium of the patient's heart, expansion of said intermediate balloon compartment is prevented from distending the patient's heart excessively.

Claims 25-30 (canceled).

REMARKS

Claims 1 – 18 and 21-24 are pending. Claims 21 – 24 are non-elected.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper, or credit any overpayment in any fees, to our Deposit Account, Number 08-3040.

Respectfully submitted,
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